REMARKS

Claims 1-7 are pending. Claims 8-24 are withdrawn pursuant to a restriction requirement. Claim 1 is currently amended.

Rejection Under 35 U.S.C. §112 Second Paragraph-Definiteness

Claims 1-7 stand rejected as indefinite for reciting the phrase "lung cancer, carcinoma" and "lung cancer carcinoma" in claim 1. The Examiner indicates that it is unclear whether the two mean the same thing.

By this amendment, claim 1 has been amended to remove the errant comma. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §112 First Paragraph-Enablement

Claims 1-7 stand rejected for lacking enablement. The Examiner contends that practicing the claimed method would require undue experimentation by a skilled artisan. The Examiner cites a reference authored by the present inventor (Wang et al., Human Pathology. 2002; 33: 921-26) which allegedly teaches that other lung carcinomas, such as bronchioloaveolar carcinoma, adenocarcinoma, adenosquamous carcinoma, and large cell carcinoma also express p63. Thus, the Examiner concludes that detecting p63 would only indicate that the lung carcinoma is not small cell or carcinoid, but would not definitively distinguish whether the carcinoma was adenocarcinoma or a differentiated squamous carcinoma as per the claims.

By this amendment, claim 1 has been amended to recite that the p63 staining in differentiated squamous carcinoma cells is uniform. This amendment is supported in the specification at pages 22-23 by the following excerpt (emphasis not original):

> The results of the current study indicate that p53 homolog p63 stains poorly differentiated squamous cell carcinomas in a **consistent** and uniform manner with very high percentages (approaching 100%) of tumor cells showing nuclear staining. Staining in well differentiated squamous cell carcinomas is also observed to be strong but is apparent in basalar, para-stromal areas lacking keratinization. Staining of other lung tumor types revealed no staining in undifferentiated small-cell carcinomas and bronchioloalveolar carcinomas, and essentially negligible staining in carcinoids...Adenocarcinomas showed varied staining patterns. When positive, the patterns differed from the staining pattern seen in squamous carcinomas.

It is submitted that the term "consistent" encompasses the consistent, uniform staining in poorly differentiated squamous carcinomas, **and** the strong staining in basalar, parastromal areas in well differentiated squamous carcinomas, and is readily distinguished from the "varied" staining patterns in adenocarcinomas. Moreover, the Wang et al. reference cited by the Examiner supports that the adenocarcinoma p63 staining was "rare, focal, or multifocal with positively stained cells admixed with p63 negative cells" and "contrasted with positively stained regions in squamous carcinomas" (page 924, col. 1, 2nd ¶). Lastly, the present specification indicates that 8 of 8 bronchioalveolar carcinomas were negative for p63 (page 21, ll. 14-15).

Accordingly, it is asserted that the method recited in claim 1 distinguishes differentiated squamous carcinomas from both undifferentiated carcinomas and adenocarcinomas and other carcinomas. Withdrawal of this rejection is respectfully requested.

The Examiner also takes issue with the fact that p63 has six isoforms, three of which contain transactivation (TA) domains and have tumor-suppressor activity instead of pro-oncogenic activity. She supports her contention with a reference to p63 on OMIM, and an article by Wu et al. (Cancer Res. 2003; 63: 2351-7). The Examiner concludes that these teachings imply that a lung cancer might not overexpress the tumor-suppressing isoforms containing the TA domain.

The Examiner is correct in noting that the definition of p63 on page 6 of the present specification, which refers to the p63 isoforms, encompasses all 6 isoforms, including the three lacking the TA domain ((emphasis not original):

> As used herein, the term "p63" refers to a protein homologous to the tumor suppressor protein p53, which contains a multi-functional DNA-binding protein important in cell cycle and cell death regulation. p63 exists in three isoforms, each of which can encode two categories of transcripts under the control of two alternative promoters. The first encodes full length proteins with an acidic N-terminal transactivation domain that, like p53, can activate transcription and induce apoptosis. The second encodes truncated proteins lacking the N-terminal transactivation domain (ΔNp63), and potentially acting in a dominant-negative manner to suppress transactivation by p53 and full length p63. Unless otherwise specified, p63 means any of the three isoforms. The three p63 splice forms, α, β, and γ may be differentially expressed in tumors.

Examiner has the opinion that this definition "clearly indicates that p63 encompasses all six isoforms," and notes that the specification teaches that the antibody used reacts against all p63 subtypes.[1]

While the Applicants do not precisely understand the nature of the Examiner's rejection, it appears that the Examiner is rejecting the claims on the basis that it is not clear which p63 isoform is present in the tumor cells evaluated according to the present invention. Applicants take the position that the isoform present in the tumor cell is irrelevant. The invention describes diagnostic differentiation based on the consistent presence, or absence, of p63, regardless of the isoform. As the Examiner herself indicated, it would be highly unlikely for an alleged "tumor-suppressing" p63 isoform even to be expressed in a squamous cell carcinoma. In addition, the presence of this isoform would not be a very effective tumor suppressor considering the

[1] We note that the antibody 4A4 from Santa Cruz described in the application was raised against the N-terminus of the *truncated* p63 of human origin (ΔNp63; see enclosed product specification sheet), not the N-terminus of full length p63. The OMIM reference cited by the Examiner clearly teaches that the acidic N-terminus of p63 contains the TA domain. Thus, the 4A4 antibody would detect all six isoforms as the definition encompasses.

specimens evaluated for diagnosis are tumor cells. Moreover, the cited OMIM reference indicates that the predominant p63 isoforms in epithelial tissue are the oncogenic, truncated forms which lack the TA domain, and it further states that "no evidence of a tumor suppressor activity was found."

Lastly, assuming *arguendo* that the present invention detected expression of the TA domain containing isoforms, this does not imply that there would be lack of expression of the other isoforms, i.e., the pro-oncogenic TA domain-lacking isoforms, i.e., (ΔNp63). As the Examiner notes, the 4A4 antibody recognizes all six forms and would not distinguish between them. However, as stated above, the present claims are not directed to distinguishing among the six isoforms of p63, the present invention is directed to distinguishing the presence or absence of the protein, which is fully enabled by the present specification.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: April 15, 2005

Respectfully submitted,

By

Stephanie R. Amoroso, Ph.D.
Registration No.: 51,401
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant